REMARKS

Inventorship

Submitted herewith is a request to correct inventorship pursuant to 37 C.F.R. 1.48(b). The amendment and/or cancellation of claims during the prosecution of this application has necessitated deletion of the names of James J. Claus and Francesca Cole. The inventors of the pending claims are Leonard P. Guarente, Nicanor Austriaco, Jr., and Brian Kennedy.

Information Disclosure Statement

The Applicants submit a supplemental information disclosure statement herewith. This statement includes issued U.S. patents to which this application claims priority. Although the present application was filed as a divisional application, the pending claims may not have been the subject of prior restriction requirement(s).

Rejection under § 112 ¶ 2

The Examiner has rejected claim 13 and claims dependent therefrom as indefinite because of the phrase "is a function of stress survival." The Applicants have amended claim 13 according to the Examiner's suggestion.

The Term "Agent"

In paragraph 6 of the Action dated April 18, 2003, the Examiner has interpreted the term "agent" to exclude mutagens:

> 6. For the purpose of examination the term "agent" in claim 13 as defined on page 31 of the specification is interpreted to exclude mutagens.

The Applicants disagree. In some instances, an agent can be a mutagen. The claimed methods that recite "an agent" are not limited to agents other than mutagens. Claim 13 had been amended to clarify that the cells are evaluated in the presence of the agent. In contrast, genetic

screens for new mutations generally involve mutagenizing cells with a mutagen, growing the cells out, in the absence of the mutagen, and, then, evaluating the cells.

The method of claim 37 requires that the modulation of replicative capacity is due to presence or absence of the agent, as opposed to a mutation induced by the agent.

Rejection under § 102(a)

The Examiner has rejected claims 13, 21, and 29 in view of Fleming et al. As mentioned above, claim 13 has been amended to include a limitation of claim 19. The Applicants respectfully request that the rejection under § 102(a) be withdrawn as moot in view of the amendment to claim 13.

Rejection under § 103 in view of Fleming

The Examiner has rejected claims 13 and 15 in view of Fleming et al. Again, claim 13 has been amended to include a limitation of claim 19. Accordingly, the Applicants respectfully request that the rejection under § 103(a) be withdrawn as moot in view of the amendment to claim 13.

The Examiner stated in paragraph 11 of the last Action:

> Fleming et al. does not show the method of claim 15 in which cells treated with an agent are stressed by heat shock and length of survival is measured.

As the Examiner points out, Fleming does not teach evaluating survival of a cell treated with an agent while the cell is under stress. Furthermore, Fleming neither teaches nor suggests that a stress survival phenotype can be correlated with replicative capacity. In other words, Fleming does not recognize a connection between stress survival and replicative capacity or that such a connection could be used to evaluate an agent for its ability to alter lifespan.

Rejection under § 103 in view of Fleming and Lundblad

The Examiner has rejected claim 19 as obvious over Fleming in view of Lundblad. The Examiner asserts:

> Fleming does not show direct measurement of mitotic potential or use of yeast cells. Lundblad et al. shows in the abstract that yeast cells mutated in the EST1 gene have a shortened lifespan. Lundblad et al. shows on page 637 the treatment of cells with defective EST1 genes. Lundblad et al. shows measurement of mitotic potential in yeast strains in figures 3 and 6 and in the experimental procedures section on pages 641-642 for the purpose of determining the effect of introduced mutations on mitotic potential.
>
> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Fleming et al. by the use of the yeast cells and mitotic potential methods of Lundblad et al. because such a modification would allow for further insights into the role of SOD [super oxide dismutase] and ageing in yeast cells.

The Applicants disagree. There is no motivation to combine Fleming and Lundblad. Moreover, neither reference recognizes a connection between stress survival and replicative capacity or that such a connection could be used to evaluate an agent for its ability to alter lifespan.

Fleming suggests that the phenotypes of overexpressed bovine SOD are within the rubric of a "free radical theory of aging." This theory posits that cells survive by defending against damage by free radicals. The theory has been used, at least, to describe the survival of non-dividing cells, such as terminally differentiated cells. Fleming states, for example, at page 269, column 1:

> As a first approximation, the free radical theory of aging predicts that the lifespan of organisms with similar metabolic rates should be correlated to their level of antioxidant defenses. [emphasis added]

Fleming concludes on page 277, column 1:

> Resistance to oxidative stress, such as that induced by thermal shock, is drastically reduced in senescent flies and correlates with the increased protein damage generated in old flies by stress and/or insufficient protection from cellular defense systems. [emphasis added]

Thus, Fleming adheres to a theory that cells die because of accumulated damage to proteins, rather than, e.g., a genetic program that modulates stress survival and replicative capacity.

Moreover, Fleming does not teach or suggest that the altered lifespan seen when bovine SOD is overexpressed can be attributed to an altered replicative capacity. For example, the Examiner notes in paragraph 12 of the last Action (line 18-19):

> Fleming does not show direct measurements of mitotic potential . . .

Likewise, Lundblad does not teach or suggest a nexus between replicative capacity and a stress survival phenotype. Lundblad states on page 640, column 2:

> [T]he eventual senescence phenotype is a direct consequence of loss of essential sequences from the telomere, leading to chromosomal loss and cell death.

There is no discussion of stress survival here since Lundblad attributes senescence to chromosomal loss. Further, Lundblad distinguishes this phenotype from a metabolic effect on page 641, column 1 (final paragraph):

> It is formally possible that an *est1*$^-$ mutation could alter some other aspect of cellular metabolism, such that the telomere-related phenotypes are a secondary consequence of this mutation. The fact that *EST1* is not essential for short-term mitotic growth argues against the possibility that *EST1* plays some central role in cellular metabolism.

Since Lundblad teaches that the replicative defects of *est1*$^-$ mutants are contrary to a "central role in cellular metabolism," one cannot conclude that, from Lundblad, one would be motivated to attribute telomere related senescence to a stress survival phenotype. Thus, Lundblad does not support a nexus between replicative capacity and a stress survival phenotype. Meanwhile, as discussed above, Fleming's "free radical theory of aging" also does not suggest a nexus between replicative capacity and a stress survival phenotype.

The Examiner has not provided any basis for combining Fleming and Lundblad except for the conclusory assertion that this combination of references "would allow for further insights into the role of SOD and ageing in yeast cells."

For "further insights" into Lundblad's observations on telomeres, having disavowed any connection to cellular metabolism, one would not evaluate defenses against free radicals or other cellular stresses. Conversely, for "further insights" into Fleming, whose theory has no relation to

mitosis, one would not be motivated to diverge from evaluating damage by free radicals and other cellular stresses to investigate replicative capacity. Because the Examiner's combination appears to be a hindsight reconstruction based on the Applicants' disclosure, the Applicants respectfully request that obviousness rejection based on Fleming and Lundblad be withdrawn.

The applicants do not concede any positions of the examiner that are not expressly addressed above, nor do the applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

Enclosed is a $270 check for excess claim fees and a $950 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket number 13407-017005.

Respectfully submitted,

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